Eur J Vasc Endovasc Surg **26**, 418–422 (2003)
doi: 10.1016/S1078-5884(03)00177-1, available online at http://www.sciencedirect.com on SCIENCE DIRECT®

Systemic Levels of Cotinine and Elastase, but not Pulmonary Function, are Associated with the Progression of Small Abdominal Aortic Aneurysms

J. S. Lindholt,[1*] B. Jørgensen,[2] N. A. Klitgaard[2] and E. W. Henneberg[3]

[1]*Department of Vascular Surgery, Rigshospitalet, University of Copenhagen, Denmark and*
[2]*Departments of Clinical Biochemistry, and* [3]*Vascular Surgery, Viborg Hospital, Denmark*

Objective: *to study whether smoking and impaired pulmonary function are associated with the expansion of abdominal aortic aneurysms (AAA).*
Methods and material: *seventy-nine men with small (3–5 cm), screen-detected AAA underwent a simple 5-step smoking history, measurement of the forced first second expiratory volume (FEV1), venepuncture and annual ultrasound scan for mean follow-up period of 3.5 years.*
Results: *all but one patient had a significantly reduced FEV1 ($p < 0.05$, Mann–Whitney). The FEV1/expected FEV1 ratio (rFEV1) was not related to AAA expansion but was negatively correlated with P-elastase-α_1-antitrypsin-complexes (P-Elastase). P-Elastase was positively correlated with smoking and S-cotinine. Smoking, S-cotinine, and P-elastase were positively correlated with the mean annual AAA expansion rate but not rFEV1.*
Conclusion: *in general, patients with AAA have impaired pulmonary function. A simple five step smoking classification is as predictive of AAA-expansion as S-cotinine. Smoking may cause elastase secretion leading to pulmonary and aortic elastin degradation but the lack of association between AAA-expansion and rFEV1 suggest that other mechanisms are important.*

Key Words: Abdominal aortic aneurysms; Surveillance; Pathogenesis; Smoking; Pulmonary function.

Introduction

Patients with chronic obstructive pulmonary disease (COPD) are more likely to have abdominal aortic aneurysms (AAA) and AAA in such patients may be more prone to rupture.[1–12] The link may be related to the degradation of elastic tissue by elastase in the lungs and the aorta as a result of smoking.[13–22] Specifically, smoking inhibits α_1-antitrypsin, the major inhibitor of elastase, and stimulates elastase secretion from the neutrophils. The U.K. small aneurysm trial showed a relationship between decreasing FEV1 and AAA rupture[23] and smoking is clearly associated with the development,[6,9,11,24,25] and possibly the expansion and rupture, of AAA.[26,27] The aim of the present study was to examine the relationship between smoking history, serum markers of nicotine consumption (cotinine),[28] lung function, serum markers of elastolysis and AAA expansion in a series of patients with small, screen-detected AAA.

Material and Method

The Viborg country AAA screening programme has been described previously.[7] Seventy-nine of all 110 small (3–5 cm), screen-detected AAA in 1994, who attended at least one annual control scanning were randomly selected to undergo a simple 5-step smoking history, measurement of the forced first second expiratory volume (FEV1),[29] venepuncture and annual ultrasound scan for mean follow-up of 3.5 years. The relative FEV1 (rFEV1) was defined as actual FEV1/predicted FEV1.[30] The mean annual expansion was calculated as: ((Present anteriorposterior (AP)-diameter—Initial AP-diameter)/days of observation)*365.25 days. The two observers[31] were blind to the results from the blood-samples. S-α_1-antitrypsin, P-elastase–α_1-antitrypsin-complexes (P-Elastase) (non-commercial ELISA), and S-Cotinine (RIA, Diagnostic Products Corp., LA, U.S.A.) were determined by

The paper was presented at the American Association for Vascular Surgery 50th Scientific Meeting and The Society for Vascular Surgery 56th Annual meeting, June 9–12, 2002, at the Hynes Convention Center in Boston, MA, U.S.A.
*Corresponding author. J. S. Lindholt, Department of Vascular Surgery RK3111, Rigshospitalet, Blegdamsvej 15, DK-2100 Copenhagen Ø.

1078–5884/000418 + 05 $35.00/0

Table 1. Medians and interquartiles of the various analysed parameters among those selected for the study and those who were not selected to the study.

	Selected study group $n = 79$			Non-selected group $n = 31$			p-value
	25th Quartiles	Median	75th Quartiles	25th Quartiles	Median	75th Quartiles	
Age (years)	67	69	71	66	68	70	0.15
AAA-size (mm)	31	33	39	30	32	38	0.40
Expansion rate (mm/year)	0.93	2.34	3.83	0.54	2.23	5.48	0.87
Systolic BP (mmHg)	140	160	170	150	160	175	0.38
Diastolic BP (mmHg)	85	90	100	90	100	100	0.43
ABI* (per cent)	81	100	114	85	100	116	0.52
rFEV1 (per cent)	52.0	72.5	91.5	53.0	77.0	86.0	0.96
Smokers (per cent)		37.5			39.2		0.87

p-values from a non-parametric comparison of these two subgroups are shown in the right column.
*ABI = Ankle brachial blood pressure index.

standard methods as previously described.[18,32,33] Smoking habits were classified as: 0 = never or former smokers, 1 = 1–10 cigarettes daily, 2 = 11–20 cigarettes daily, 3 = above 20 cigarettes daily. All others, e.g., smokers with a mixed consumption of pipe, cigars, and cigarettes, were ranked 4 based empirically upon the median cotinine levels. The trial was approved by the local scientific ethics committee and reported to the Central Control of Registers. SPSS 10.0 was used for non parametric tests, Spearman's correlation, Mann–Whitney, and Kruskal–Wallis.[34]

Results

Demographic data of the selected and unselected cases are presented in Table 1 showing no apparent differences. The median annual AAA expansion was 2.3 mm, FEV1 was 2.25 (interquartile range [IQR] 1.56–2.88), and the rFEV1 was 0.70 (IQR 0.46–0.93). All of the patients bar one had a FEV1 significantly below expected ($p < 0.05$, Mann–Whitney). The smoking scale correlated significant positively with S-Cotinine, P-Elastase, S-α_1-antitrypsine, and expansion rate but not with rFEV1 (Table 2). S-Cotinine also correlated with P-Elastase, S-α_1-antitrypsin, and expansion rate (Fig. 1) but not with rFEV1 (Table 3). P-Elastase also correlated negatively with rFEV1, positively with expansion rate (Fig. 2) and S-α_1-antitrypsin (Table 3). Finally, rFEV1 and mean annual expansion rate did not correlate ($r = 0.13$, $p = 0.26$) (Table 3, Fig. 3).

Discussion

All patients bar one had impaired lung function.[30] The

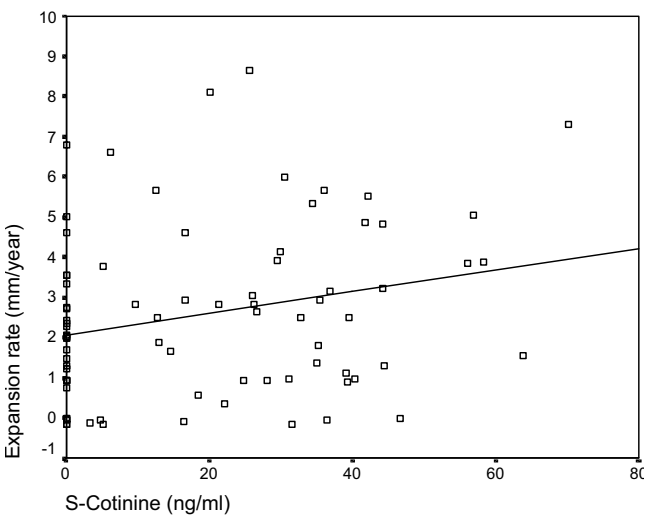

Fig. 1. Scatter plot of serum level of S-Cotinine and the expansion rate of small abdominal aortic aneurysms. Spearman's correlation coefficient $r = 0.24$ ($p = 0.04$).

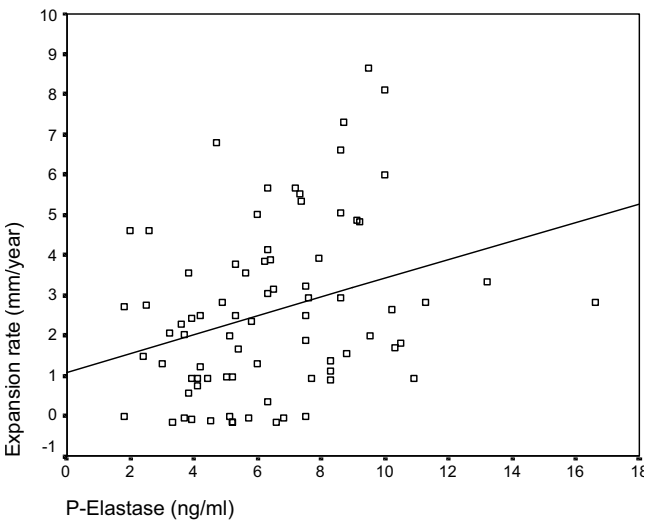

Fig. 2. Scatter plot of plasma level of P-Elastase and the expansion rate of small abdominal aortic aneurysms. Spearman's correlation coefficient $r = 0.30$ ($p = 0.0004$).

Table 2. Comparison of smoking interview data classified into a five categorical rank scale with serological markers, pulmonary function, and the size and expansion rate of small abdominal aortic aneurysms.

Smoking scale	*N*	S-Cotinine ng/ml	P-Elastase ng/ml	α_1-anti-trypsine mg/l	rFEV1 l/min	Expansion rate mm/year	Initial AAA-size mm
Non-smokers	31	33.1	50.7	1.26	2.31	1.13	34.7
<10 cig. Daily	12	259.9	69.8	1.50	2.33	2.00	34.9
10–20 cig. Daily	20	305.3	67.0	1.41	2.08	2.70	34.5
>20 cig. Daily	5	303.1	64.4	1.34	2.09	2.25	36.6
Mixed consumption	11	327.4	89.3	2.08	2.18	4.56	35.5
Kruskal–Wallis test	79	(0.000)	(0.001)	(0.015)	(0.818)	(0.011)	(0.861)
Correlation coefficient, *r* (*p*-value)	79	0.69	0.46	0.31	−0.09	0.22	0.03
		(0.000)	(0.000)	(0.006)	(0.401)	(0.048)	(0.798)

Medians with 25- and 75 percentiles. Kruskal–Wallis tests for differences between the ranks of the scale, and Spearman's correlation coeficients for correlation between the ranks. *p*-values in parentheses. Last row: Spearmann's correlation coefficients with *p*-value in parentheses.

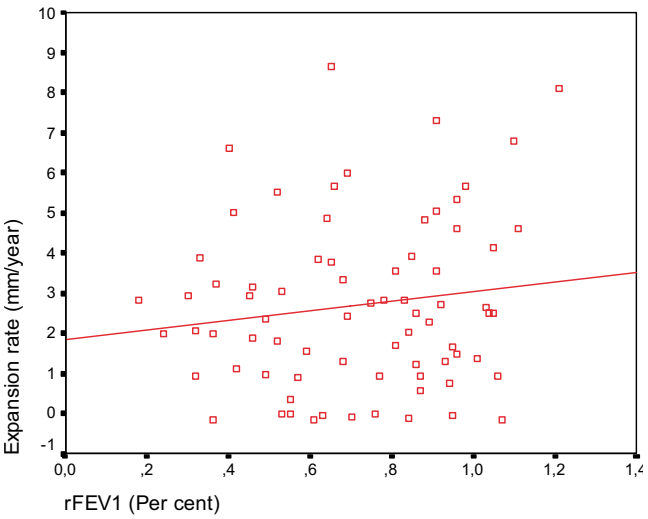

Fig. 3. Scatter plot of the relative pulmonary function and the expansion rate of small abdominal aortic aneurysms. Spearman's correlation coefficient $r = 0.13$ ($p = 0.26$).

negative correlation between FEV1 and P-Elastase suggest that this is, at least partly, caused by elastolysis. Similarly, the correlation between P-Elastase and expansion implicates elastolysis in aneurismal degradation. Perhaps surprisingly, therefore, there was no correlation between FEV1 and expansion. This may be because elastase plays a major role in the pulmonary disease but only a small role in AAA, where other proteases such as plasmin, metalloproteinases, and cysteine protheases are also active.[35–40]

As cotinine has a half-life of about 18 h (cf. 2 h for nicotine), plasma levels are constant during the smoking hours. As urinary continue needs to be creatinine-adjusted the measurement of plasma cotinine is preferable.[41–44] The simple 5-step smoking history obtained at interview was just as closely associated with AAA expansion as P-Cotinine levels, FEV1, P-Elastase, and S-α_1-antitrypsin levels. This reaffirms the importance of implementing effective smoking cessation strategies in this patient population.

To summarise, most men with AAA have impaired pulmonary function. Smoking and elastase-secretion are predictive for pulmonary and aortic elastin degradation but the lack of association between AAA-expansion and FEV1 suggests that additional mechanisms are at work in the matrix degradation of the aorta causing AAA.

Table 3. Correlation matrix of mean annual expansion rate, relative pulmonary function (rFEV1) and serological markers.

	Smoking	S-Cotinine	P-Elastase	rFEV1
S-Cotinine (ng/ml)	0.69 (<0.01)			
P-Elastase (ng/ml)	0.46 (<0.01)	0.48 (<0.01)		
rFEV1 (1/min)	−0.07 (0.57)	−0.14 (0.24)	−0.23 (0.05)	
α_1-antitrypsin (ng/ml)	0.31 (<0.01)	0.37 (<0.01)	0.28 (0.01)	−0.17 (0.15)
Expansion rate (mm/year)	0.23 (0.04)	0.24 (0.04)	0.30 (<0.01)	0.13 (0.26)

Spearman's correlation coefficients. *p* values in parentheses. rFEV1 = Observed FEV1/expected FEV1.

Acknowledgements

Nurse A. K. Sahlholdt, Dr P. Jaeger, and Dr S. Vammen are thanked for committed assistance. The Health Department of Viborg County, The Danish Heart Foundation, The Danish National Council of Health Research, The Foundation of Health Research in Western Denmark, and The Foundation of Rosa and Asta Jensen are thanked for economical support.

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Accepted 24 March 2003